Study shows how stem cell therapy protects bone in lupus

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Songtao Shi

People with lupus, an autoimmune disease, suffer from fatigue, joint pain and swelling and also have a markedly increased risk of developing osteoporosis. Clinical trials have shown that receiving a transplant of mesenchymal stem cells can greatly improve the condition of lupus patients, yet it has not been clear why this treatment strategy works so well.

Now, University of Pennsylvania researchers and colleagues have

puzzled out a mechanism by which stem cell transplants may help preserve bone in an animal model of lupus. In a paper published in the journal *Cell Metabolism*, they show that the transplanted cells provide a source of a key protein called Fas, which improves the function of bone marrow stem cells through a multi-step, epigenetic effect. The work has implications for potential therapeutic strategies for lupus as well as other diseases for which stem cell transplants have shown promise.

"When we used stem cells for these diseases and put them into the circulation, we didn't know exactly what they were doing but saw that they were very effective," said Songtao Shi, chair and professor of the Department of Anatomy and Cell Biology in Penn's School of Dental Medicine and a co-corresponding author on the paper. "Now we've seen in a model of lupus that bone-forming mesenchymal stem cell function was rescued by a mechanism that was totally unexpected."

Shi collaborated on the work with Shiyu Liu, Dawei Liu, Chider Chen and Ruili Yang of Penn Dental Medicine; Kazunori Hamamura, Alireza Moshaverinia and Yao Liu of the University of Southern California; and co-corresponding author Yan Jin of China's Fourth Military Medical University.

Shi and colleagues had earlier shown that mesenchymal stem cells can be used to treat various autoimmune conditions in animal models. The success was welcome, but the researchers didn't quite understand why the method was so successful.

"We found that a one-time injection of stem cells would ameliorate disease for far longer than we would expect," Shi said.

They knew that the transplanted cells were not becoming incorporated into the recipient's organs to a significant degree, so what was allowing the effect to last? The researchers began to suspect that an epigenetic

mechanism was at work that could permanently recalibrate how the recipient's genes were being regulated to switch them from a pathogenic to a normal state.

To investigate this possibility, the team looked at a mouse model of lupus, which they had earlier shown could be ameliorated with one injection of stem cells. Normally, mice with lupus had bone marrow mesenchymal stem cells which did not differentiate normally and thus had a significantly reduced capacity to produce new bone. An infusion of stem cells reversed this abnormality, even as long as 12 weeks following the transfer.

Pursuing the possibility of an epigenetic mechanism, which could regulate how genes were expressed, the researchers then analyzed patterns of DNA methylation acting on the promoters of bone marrow mesenchymal stem cell genes. They found that the lupus mice had a significant different pattern than normal mice, a difference that was partially reversed by stem cell therapy.

Further experiments allowed the researchers to piece together the pathway by which this occurred. They found that genes in the Notch family, genes known to be involved in bone stem cell self-renewal and differentiation, became highly methylated in the promoter region when mice with lupus received stem cell infusions. Eventually they discovered that the lupus mice had a malfunctioning Fas protein that prevented their bone marrow mesenchymal stem cells from releasing a microRNA molecule, which in turn blocked methylation of the Notch promoter. As a result, the lupus mice's stem cells differentiated poorly, and they had weaker bones.

When a stem cell infusion from a healthy donor was introduced, however, the donated cells secreted microvesicles called exosomes containing normal versions of Fas that could be used and reused by the

diseased cells, restoring their ability to self-renew and differentiate and promoting bone formation. Indeed, Shi's team demonstrated that Fas alone, delivered by secreted exosomes, could rescue the activity of lupus bone marrow stem cells in culture.

"The cells themselves don't produce Fas, but they can use the components of the donor stem cells to rescue their function," he said.

To see if this process is common across different conditions, Shi and colleagues are now exploring the mechanisms by which stem cell therapies reap benefits in other models of disease.

"You can imagine if you can reuse Fas you might also be able to reuse other cell components to target other diseases," Shi said.

More information: Shiyu Liu et al. MSC Transplantation Improves Osteopenia via Epigenetic Regulation of Notch Signaling in Lupus, *Cell Metabolism* (2015). DOI: 10.1016/j.cmet.2015.08.018

Lingyun Sun et al. Mesenchymal Stem Cell Transplantation Reverses Multiorgan Dysfunction in Systemic Lupus Erythematosus Mice and Humans, *Stem Cells* (2009). DOI: 10.1002/stem.68

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